APPENDIX A

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 021123-0273989

In re Application of BETTINA MOCKEL, ET AL

Application Number: 09/725,178 — Filed: November 29, 2000

For NOVEL NUCLEOTIDE SEQUENCES ENCODING THE GPM GENE

Group Art Unit: 1645 — Examiner: R. Huston

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☐	One month (37 CFR 1.17(a)(1))	$
☒	Two months (37 CFR 1.17(a)(2))	$ 410.00
☐	Three months (37 CFR 1.17(a)(3))	$
☐	Four months (37 CFR 1.17(a)(4))	$
☐	Five months (37 CFR 1.17(a)(5))	$

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $_____.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 033975. I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a)_____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

September 22, 2003
Date

Thomas A Cawley Jr
Signature

Thomas A. Cawley, Jr.
Reg. No. 40944
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

Burden Hour Statement: This form is estimated to take 0.1 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Mockel *et al.*

Group Art Unit: 1652

Appln. No.: 09/834,722

Examiner: R. Hutson

Filed: November 29, 2000

Title: Novel Nucleotide Sequences Encoding the Gpm Gene

September 22, 2003

* * * * *

AMENDMENT "B" AND RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the official action dated April 22, 2003, wherein the pending claims were rejected pursuant to 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §102(b). The applicants respectfully traverse in view of the following amendments and remarks.

I. AMENDMENT TO THE CLAIMS

Claim 1. (Previously Amended) An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide encoding a polypeptide containing an amino acid sequence which is at least 90% identical the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate mutase activity, and

b) a polynucleotide that is complementary to the polynucleotide of (a).

Claim 2. (Previously Amended) The isolated polynucleotide according to claim 1 wherein said polynucleotide is isolated from a coryneform bacterium.

Claim 3. (Cancelled)

Claim 4. (Currently Amended) The polynucleotide according to claim 2 containing the nucleic acid sequence as shown in SEQ ID NO: 1.

Claim 5. (Allowed) An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide containing the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate mutase activity, and

(b) a polynucleotide that is complementary to the polynucleotide of a), the polynucleotide encoding a polypeptide having phosphoglycerate mutase activity.

Claim 6. (Currently Amended) An isolated polypeptide consisting of: the nucleotide sequence shown in SEQ ID NO: 1, or a fragment thereof, wherein said nucleotide sequence or fragment thereof encode for a polypeptide having phosphoglycerate mutase activity.

Claim 7. (Allowed) An isolated corynebacterial polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide that is identical to SEQ ID NO: 1 encoding a polypeptide containing the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate mutase activity,

(b) a polynucleotide that is complementary to the polynucleotide of (a), encoding a polypeptide having phosphoglycerate mutase activity.

Claim 8-21. (Cancelled)

Claim 22. (Previously Amended) A member of the coryneform group of bacteria transformed by the polynucleotide according to one of claims 1, 5, 6, or 7.

Claim 23. (Previously Amended) Bacteria according to claim 22, wherein the bacteria are of the genus Corynebacterium.

Claim 24. (Cancelled)

Claim 25. (Cancelled)

Claim 26. (Cancelled)

Claim 27. (New) An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide encoding a polypeptide containing an amino acid sequence which is at least 95% identical the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate mutase activity, and

b) a polynucleotide that is complementary to the polynucleotide of (a).

Claim 28. (New) A vector comprising the polynucleotide of 1, 5, 7, or 27.

Claim 29. (New) The vector of claim 28, wherein said vector is an expression vector.

Claim 30. (New) A vector that is an expression vector pXKgpmexp comprising

(a) the polynucleotide of claims 5 and 7; and

(b) a restriction map as set forth in Figure 2.

Claim 31. (New) A host cell comprising the vector of claim 28.

Claim 32. (New) A host cell of claim 31 that is a prokaryotic cell.

II. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 5 and 7 have been allowed. Claims 1, 2, 4, 6, 21-23, 25 and 26 are at issue.

Amended claim 6 is directed to an isolated polynucleotide consisting of the nucleotide sequence shown in SEQ ID NO: 1, or a fragment thereof, wherein said nucleotide sequence or fragment thereof encode for a polypeptide having phosphoglycerate mutase activity. Support for amended claim 6 can be found throughout the specification, for example, on page 9, line 1 to 3 and Examples 4 and 5.

New claim 27 is directed to an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a polynucleotide encoding a polypeptide containing an amino acid sequence which is at least 95% identical the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate mutase activity, and a polynucleotide that is complementary to the polynucleotide of (a). Support for new claim 25 can be found throughout the specification, for example, on page 5, lines 20-27.

New claims 28-32 recite the polynucleotides of claims 1, 5, 7, or 27 in vectors and host cells. Support for these new claims can be found throughout the specification, for example, on page 4, lines 9-14; page 11, line 9 through 32; Figure 2; and page 15, line 27 to page 16, line 9.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, First Paragraph, Written Description

The examiner rejected claims 2, 24, and 25 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Specifically, the examiner alleged that the specification does not adequately describe the genus of the "naturally occurring" polynucleotides encoding a polypeptide that has at least 90% identity to SEQ ID NO: 2, the polypeptide having

phosphoglycerate mutase activity, so that one of skill in the art would be able to predict naturally occurring sequences, particularly in view of the larger genus that includes both naturally and "manufactured" sequences. The applicants respectfully traverse.

Solely for the purpose of expediting prosecution, and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have cancelled claims 24 and 25 without prejudice, thereby obviating the rejection of these claims.

Claim 2 is directed to the isolated polynucleotide according to claim 1 wherein said polynucleotide is isolated from a coryneform bacterium. Claim 1 and new claim 27 is directed to an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a polynucleotide encoding a polypeptide containing an amino acid sequence which is at least 90% (or 95% identical in claim 27) identical to the amino acid sequence of SEQ ID NO: 2, the polypeptide having phosphoglycerate activity and a polynucleotide complementary to the polynucleotide of (a). These structural and functional characteristics of the subject matter meet the Written Description Guidelines of the United States Patent Office (February, 2000). In particular, Example 14 of the guidelines states that a claimed variant polynucleotide that has a high percent identity to a sequence taught in the specification, along with a functional limitation that the claimed variant polynucleotides encode variant polypeptides that exhibit a specified catalytic activity, meet the written description if the required activity can be determined in the specification. With regard to determining a function of the variant polypeptide, procedures or assays that measure for well known enzymatic reactions (i.e., the phosphoglycerate mutase conversion of 3-phosphoglycerate to 2-phosphoglycerate) do not require explicit description in the specification. For example, the guidelines further teach "an absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. § 112, first paragraph, for lack of adequate written description." (See page 4, lines 18-24 of the Written Description Guidelines).

The issue raised by the examiner is whether the specification adequately describes 90 or 95% variants with phosphoglycerate mutase activity. In the instant claims, the claimed variants must each be at least 90% or 95% identical to the amino acid sequence of SEQ ID NO: 2 and encode a polypeptide that retains the specified phosphoglycerate mutase activity (see page 5, lines 20-27; page 7, lines 11-13). The applicants respectfully submit that assaying for phosphoglycerate mutase activity was a "well-established procedure" in the art

at the time of filing (see Kuhn *et al., Biochemistry and Biophysics* 306:342-349, page 343, first column (1993)). Furthermore, the specification teaches an indirect assay for identifying amino acid variants encoding an active phosphoglycerate mutase (see Example 5, Table 1, and page 10, lines 1-3).

Specifically, the applicants have discovered overexpression of the gpm gene (in a lysine producing *C. glutamicum* strain) increases the production of L-lysine. Example 5 teaches how to measure the quantity of lysine after fermentation in order to compare *C. glutamicum* strains that overexpress gpm versus wild-type (no overexpression of gpm). In view of table 1 of Example 5, one of skill in the art would appreciate the enhanced expression of a functional phosphoglycerate mutase directly increases the level of lysine production. Thus, variant polypeptides with phosphoglycerate mutase activity can be assayed for according to the teachings of Example 5 by measuring for lysine production.

Accordingly, the structural and functional limitations of claim 2 (via claim 1) and new claim 27 are described in the specification in such a way as to convey to one of skill in the art that the applicants had possession of a finite number of claimed polynucleotides.

In view of the foregoing remarks, the applicants submit that the rejection of claim 2 pursuant to 35 U.S.C. § 112, first paragraph, for lack of written description, is moot, and a rejection of new claim 27 on the same grounds would be improper.

Rejection Pursuant to 35 U.S.C. §112, First Paragraph, Enablement

On page 5 of the official action, the examiner rejected claims 1, 2, 4, and 21-23 under 35 U.S.C. § 112, first paragraph, for lacking enablement. Specifically, the examiner asserted that while the specification is enabling for a polynucleotide encoding a polypeptide which has the amino acid sequence of SEQ ID NO: 2, wherein said polypeptide has phosphoglycerate mutase activity, [the specification] does not reasonably provide enablement encoding a polypeptide which is a mere 90% identical to SEQ ID NO: 2, wherein said polypeptide has phosphoglycerate mutase enzymatic activity. The examiner further alleged the specification does not support the broad scope of the claims which encompass the claimed modifications or fragments of SEQ ID NO: 1 because the specification does not establish (A) regions of the protein structure which may be modified without effecting phosphoglycerate mutate enzymatic activity; (B) the general tolerance of phosphoglycerate mutase enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme to modifying

any amino acid residue of a phosphoglycerate mutase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. In view of the foregoing amendment, the applicants respectfully traverse the enablement rejection.

The issue of enablement involves the question of whether an application enables one of ordinary skill in the art to make and to use the claimed invention. Experimentation is limited in claim 1 and new claim 27 because these claims are limited to nucleic acids encoding polypeptide containing an amino acid sequence which is at least 90% (or 95% identical in claim 27) identical to the amino acid sequence of SEQ ID NO: 2, that exhibits phosphoglycerate mutase (Gpm) activity. Therefore, there is no question that the variants encompassed by the claims must retain the utility of the DNA sequence discovered and claimed by the applicants. The applicants further submit the specification enables one of skill to make and functionally define the claimed variants.

Specifically, claim 1 and new claim 27 satisfy the "how to make" prong of the enablement requirement because the scope of the claim is "reasonable correlated" with the teachings in the application. The application and ordinary skill permit one skilled in the art to make any polynucleotide having 90% or greater sequence similar to the sequence recited in the claim using PCR technology (see page 9, lines 28-34 and page 20, line 18 to page 21, line 8). In fact, the Patent Office's own written description training materials acknowledge that "procedure for making variants of [a protein having] SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art." (See Revised Interim Written Description Guidelines Training Materials, Example 14). Moreover, the application provides guidance as to the types of changes (e.g., conservative mutations) that are more likely to retain functionality (See specification, page 8, line 30 to page 9, line 12).

The variants recited in claim 1 are also functionally defined in that the claimed variants are limited to those with phosphoglycerate mutase (Gpm) activity (catalyzing 3-phosphoglycerate to 2-phosphoglycerate). The specification specifically refers to the inventors successfully isolating the novel gpm gene coding for the enzyme phosphoglycerate mutase from *C. glutamicum* (page 7, lines 11-14). The specification also specifically describes the desired variant polypeptides with at least 90 to 95% identity to the polypeptide according to SEQ ID NO: 2 must have Gpm activity (page 5, lines 20-27).

Gpm activity is a routine screening assay that identifies those encoded polypeptides with the activity (phosphoglycerate mutase enzymatic activity) recited in the claims (Kuhn *et al., Arch. Biochem. Biophys.* 306:342-349 (1993); Benoit *et al., J. Bact.* 183:4702-4708, 4703 (2001)). Since the Gpm assay is routine in the art, one of skill could perform this assay without undue experimentation. For example, the Gpm assay is performed by adding 3-PGA in a reaction mixture (DPG + buffer TES) containing Gpm. The reaction is stopped after 2 minutes at 34°C by addition of tricholoracetic acid and N-ethylmaleimide. The amount of 2-PGA produced in the Gpm reaction mixture is measured by the addition of the enzymes enolase, pyruvate kinase, and lactate dehydrogenase. As these enzymatic reactions occur, the oxidation of NADH is monitored at 340 nm. The amount of NAD produced is proportional to the amount of 2-PGA added to the assay.

Finally, as discussed above, Example 5 enables one of skill in the art to directly correlate the functionality of Gpm in a 90% or higher variant by measuring lysine production in comparison to a wild type strain with no enhanced Gpm activity. Accordingly, in view of the structural and functional information about the claimed polynucleotides that is provided in the instant application along with knowledge in the art of Gpm assays that is well known to one of ordinary skill in the art, the applicants submit that claim 1, claim 1's dependents, and newly added claim 27 are supported by an enabling disclosure.

In order to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, claim 21 has been cancelled without prejudice thereby obviating the rejection of this claim. Claims 2, 4, 22, and 23 are ultimately dependent upon claim 1 and therefore are also fully enabled by the specification.

In light of the foregoing amendments and remarks, the applicants submit that the rejection of claims 1, 2, 4, and 21-23 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome and should be withdrawn, and a rejection of new claim 27 on the same grounds would be improper.

Rejection Pursuant to 35 U.S.C. §102(b), Anticipation

On pages 9 of the office action, the examiner rejected claim 6 under 35 U.S.C. § 102(b) as being anticipated by Sigma Catalog, 1997, page 1019. Specifically, the examiner alleged the Sigma catalog teaches a number of di-, tri- and polynucleotide molecules which

are encompassed by fragments of SEQ ID NO: 1 and claim 6 was drawn to fragments without the phosphoglycerate mutase activity limitation.

The applicants respectfully traverse and submit that these rejections are now moot in view of the foregoing amendment to the claims. Amended claim 6 is now directed to an isolated polypeptide consisting of the nucleotide sequence shown in SEQ ID NO: 1 or a fragment thereof, wherein said nucleotide sequence or fragment thereof encode for a polypeptide having phosphoglycerate mutase activity. Amended claim 6 now requires the nucleotide sequence SEQ ID NO: 1 and the fragment thereof must have phosphoglycerate mutase activity which is neither disclosed nor suggested by the document cited by the examiner. Accordingly, the applicants respectfully submit the rejection of claim 6 under 35 U.S.C. §102(b) is overcome and should be withdrawn.

CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the Examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
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